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(54) **Flash-melt oral dosage formulation**

In der Mundhöhle schnell zerfallende orale feste Verabreichungsform

Forme de dosage orale très fondante

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EP 1 145 711 B1

Description

Field of the Invention

[0001] The present invention relates to a flash melt pharmaceutical oral dosage form that disperses in the mouth in under about 25 seconds.

Background of the Invention

[0002] There are a number of varieties of solid pharmaceutical dosage forms that rapidly dissolve or disintegrate in a glass of water, in the mouth, or in the gastrointestinal tract. Such dosage forms have been known in the art for many years. The obvious advantages of the convenience of carrying dosage forms that will dissolve or effervesce in water to release medicaments are well known. Likewise, the therapeutic need of having an oral dosage form that will rapidly dissolve or disintegrate in the mouth for situations where immediate medication is necessary and water is not available has long been recognized.

[0003] Initially, a distinction must be drawn between flash-melt dosage forms and rapidly disintegrating dosage forms. The former are intended to dissolve or disintegrate in the mouth of the patient in less than one minute whereas the latter are intended for primary dissolution or disintegration within 3 to 20 minutes in the acidic medium of the stomach or a container of water. The recognized test for rapidly disintegrating dosage forms is disintegration time in 0.1 Mol/L (N) hydrochloric acid. Those of ordinary skill in the art will appreciate that the requirements for formulating dosage forms to meet these criteria must necessarily be different since the conditions, particularly pH, in the mouth and the stomach are quite different. More important, the time in which a dosage form must dissolve or disintegrate in the mouth is necessarily much shorter than in the stomach with the obvious exception of dosage forms, e.g. lozenges, that are specifically formulated to slowly dissolve in the mouth.

[0004] Another consideration common to most if not all dosage form formulations intended for flash-melt or rapid disintegration is the need to take precautions in the preparation, packaging, handling and storing of the finished dosage forms since they tend to be both hygroscopic and friable. Dosage forms dependent on effervescence to promote their disintegration are particularly susceptible to moisture and must be packaged with special wrapping, stoppers, packets of drying agent and the like.

[0005] Regardless of such potential problems, there is still an acute need for dosage forms that can rapidly dissolve or disintegrate for the obvious benefits of having a therapeutic dosage of the medicament contained therein available for absorption in a very short time. In addition to the benefits of rapid availability, flash-melt dosage forms are advantageous for administration of medicaments to patients such as the very young, the elderly, the non-compliant and those with a physical impairment that makes it difficult if not impossible to swallow an intact dosage form. Flash-melt dosage forms are further a convenience for situations where potable water may not be readily available or desirable. Medicaments amendable to such dosage forms would include sedatives, hypnotics, antipsychotics, motion sickness medication, mild stimulants such as caffeine and the like.

[0006] Those of ordinary skill in the art are aware that there are two basic compounding concepts recognized for the preparation of rapidly dissolving/disintegrating dosage forms. The first of these, particularly suited for the preparation of flash-melt dosage forms, is freeze drying wherein a cake or wafer is prepared from a freeze-dried solution or suspension of medicament and suitable excipients in water or other solvents. Such wafers dissolve very rapidly on the tongue, i.e. within about ten seconds, due to a combination of a high affinity for moisture resulting from the freeze drying process and a very high porosity, which promotes rapid ingress of saliva. While such dosage forms are capable of rapid disintegration/dissolution in the mouth, the freeze drying process suffers from several disadvantages, primary among which is the fact that a solution or a stable suspension of the medicament must be formed before it can be freeze dried. While not always the case, typically such solutions are aqueous and, therefore, not suited to formulating medicaments sensitive to water. The process itself is typically laborious and time-consuming. Finally, the resultant dosage forms, in addition to being hygroscopic, tend to be very soft and, therefore, require special moisture-and impact-resistant packaging and require careful handling prior to administration.

[0007] The second major technology utilized in the manufacture of rapidly disintegrating dosage forms is based on special grades of sugars such as mannitol, sorbitol and the like in combination with superdisintegrants. The latter are excipients that are characterized by a special wicking capacity to channel water into the interior of the dosage form, or by rapid swelling in water, both of which act to hasten disintegration. It is also known to enhance dissolution of dosage forms by the inclusion of effervescent combinations, typically sodium bicarbonate and a weak acid, such as citric acid. As noted above, effervescent formulations require special moisture resistant packaging as even very small levels of moisture may be sufficient to initiate the effervescent reaction. Techniques, such as fluidized bed granulation, are recognized as being useful in the preparation of such formulations. Too often, however, such technologies require a specific, very costly plant including special handling equipment, controlled-humidity environments and the like. In spite

of such measures, dosage forms produced by such techniques typically require moisture resistant packaging, the need to include in the packaging packets or capsules of moisture absorbing agents and the like.

[0008] An example of a teaching of the incorporation of super disintegrants in dosage form formulations to enhance dissolution is WO 98/030640, FMC Corporation. It is disclosed therein that, for cost considerations, up to 90% of a group of super disintegrants including cross-linked cellulose, cross-linked carboxymethyl cellulose, cross-linked starch, croscarmellose alkali metal salt, crospovidone, alkali metal starch - glycolate and the like can be replaced by a co-disintegrant. Included among the latter group are natural diatomaceous silica, a synthetic hydrous alkaline earth metal calcium silicate and a porous hydrophilic zeolite. The weight ratio of super disintegrant to co-disintegrant is stated as from 4:1 to 1:10, preferably 2-1:1. There is no indication of any recognition of benefits to be derived from the formulation other than the obvious consideration of cost savings since the co-disintegrants are less expensive and the combination is stated to accomplish the desired results.

[0009] In contrast, Japanese patent 10114655, Kyowa Hakko Kogyo KK discloses a formulation intended for rapid dissolution in the stomach that can contain up to 30% by weight of a superdisintegrant, such as crospovidone or hydroxypropylcellulose, croscarmellose and the like and up to 30 % of a neutral or basic ingredient including magnesium aluminum metasilicate, calcium silicate, a phosphoric acid salt or a metal hydroxide. The dosage form is intended for medicaments that produce a gel at acidic pH.

[0010] WO 98/46215 relates to a rapidly dissolvable dosage form adapted for direct oral dosing. The dosage form includes an active ingredient and a matrix which is composed of at least a non-direct compression filler and a lubricant. The dosage form is adapted to rapidly dissolve in the mouth of a patient in about 90 seconds or less and thereby liberate the active ingredient.

[0011] There are numerous other examples of specific formulations that utilize one or more of the techniques or mechanisms discussed above. For the most part, however, they also possess one or more of the enumerated disadvantages to some degree, e.g. it is difficult or expensive to produce dosage forms by such techniques, the resulting dosage forms are friable or are sensitive to environmental factors such as moisture. There continues to be the need for a formulation that mitigates or eliminates these disadvantages, yet yields a flash-melt dosage form that will disintegrate in the mouth within about 25 seconds. Such formulations are provided in accordance with the present invention

Summary of the Invention

[0012] A formulation is disclosed which is suitable for the preparation of granules without solvents that can be compressed on conventional equipment into pharmaceutical oral dosage forms, e.g. tablets, caplets, wafers and the like, that will disintegrate in the mouth in under about 25 seconds. The formulation is comprised of a suitable medicament and a four component excipient combination consisting of a superdisintegrant, a dispersing agent, a distributing agent, and binder that also functions as a wicking agent to promote ingress of fluids into the dosage form and may also include other conventional ingredients such as sweetening and flavoring agents. The combination of excipients comprises, based on the total weight of the dosage form:

a) from 4 to 8 % by weight of a superdisintegrant,
b) from 20 to 70 % by weight of a dispersing agent which is a calcium silicate,
c) from 1 to 10 % by weight of a distributing agent selected from amorphous silica, fumed silica, diatomaceous earth, talc, kaoline and magnesium aluminium trisilicate, and
d) from 10 to 50 % by weight of a binder.

[0013] The preparation of the formulation of the inventionis unique in that the combination of four excipients can be dry granulated with the medicament and suitable conventional ingredients, such as flavoring and sweetening agents, without the use of any solvent, to form stable granules that can be readily compressed into dosage forms on conventional equipment without the need for special handling techniques. In a particular embodiment, granules are formed containing the medicament and other ingredients and a majority of the excipient combination. The granules are then blended with the remaining ingredients to form a final blend suitable for direct compression into dosage forms on conventional equipment.

Detailed Description of the Invention

[0014] The formulation of the present invention and the process of preparing flash-melt dosage forms therefrom are based on a combination of four excipients. This unique combination of excipients may be formulated with other conventional adjuncts, particularly flavoring agents, sweetening agents, lubricants and the like and one or more active medicaments as will be discussed below. The active medicament may comprise up to about 30% by weight, preferably up to about 15% by weight, of the formulation, depending on the amount required for a therapeutically effective dosage

and factors such as its capacity to be directly granulated, the amount of flavoring/sweetening agents required to mask the taste or bitterness thereof and the like. It is within the scope of the present invention to utilize medicaments that are coated for taste or other reason in the subject formulations provided that the coatings do not interfere with either the compounding or the disintegration of the tablets. The excipient combination comprises, in total, up to about 85% by weight, preferably from about 50% to about 80% by weight, of the formulation.

[0015] The excipient component of the formulations of the present invention is a combination of a superdisintegrant, a dispersing agent, a distributing agent, and a binder. Suitable superdisintegrants include crospovidone, croscarmellose sodium, sodium starch glycolate, low-substituted hydroxypropylcellulose, pregelatinized starch and the like. The preferred superdisintegrant for the subject formulations is crospovidone since it can be utilized in large amounts without causing a formulation containing it to have a propensity to gel.

[0016] Suitable dispersing agents, also sometimes referred to in the art as anticaking agents, include calcium silicate-ortho, meta and alpha triclinic forms thereof. Particularly preferred is a crystalline alpha triclinic calcium silicate, commercially available from Aldrich Chemical Company which meets the following specifications: 1.3 m^2/g surface area; 0.63 g/ml bulk density; 2.90 g/ml true density; and < 1% w/w volatiles. A variety of pharmaceutical grades of calcium silicate available from other vendors, as shown in Table 1, have also been found to produce satisfactory flash-melt dosage forms as well. These include ortho and meta forms of calcium silicate available from Alfa-Aesar, synthetic calcium silicates Micro-cel C and Micro-cel E, available from Celite Corp, Hubersorb 600 NF and Hubersorb 250 NF available from J. M. Huber Corp, and combinations of various grades thereof. These products have been found to cover the following range of specifications for calcium silicate: 1.0 m^2/g to 210 m^2/g surface area; 0.075 g/ml to 0.90 g/ml bulk density; 1.70 g/ml to 2.90 g/ml true density; and < 1% to 14% w/w volatiles. Table 1 lists the individual specifications for each of the materials obtained from the vendors listed above.

Table 1.

Source	Description area	Surface m^2/g	Bulk Density g/ml (±s.d.)	True Density g/ml	Volatiles (% w/w) (% w/w)
Aldrich	CaSiO3 < 200mesh (crystalline, alpha triclinic)	1.3	0.627 (0.020)	2.934	0.50
Alfa Aesar	2CaO.SiO2 (crystalline, ortho)	0.98	0.492 (0.003)	3.252	0.02
Alfa Aesar	CaSi03 (crystalline, meta)	2.5	0.867 (0.009)	2.940	0.50
Celcite	Micro-cel E (crystalline)	90.4	0.094 (0.006)	2.596	0.94
Celcite	Micro-cel C (amorphous)	191.3	0.120 (0.006)	2.314	5.11
JM Huber	Hubersorb 250NF (amorphous)	103.0	0.130 (0.008)	1.702	9.90
JM Huber	Hubersorb 600NF (amorphous)	209	0.075 (<0.001)	2.035	13.8

[0017] Alpha triclinic calcium silicate is advantageously combined in the subject formulations with at least one other pharmaceutical grade of calcium silicate wherein the alpha triclinic form would comprise from about 10% to about 90% by weight of the combination. In contrast to its use in conventional tabletting formulations, it is considered unexpected that the dispersing agent, i.e. calcium silicate, is the primary constituent of the excipient combination of the subject formulations since it is generally recognized by those of ordinary skill in the art as being poorly compressible.

[0018] The distributing agents for the excipient combination of the subject formulations include amorphous silica, fumed silica, diatomaceous earth, talc, kaolin, magnesium aluminum trisilicate and the like, with amorphous silica being especially preferred.

[0019] The final component of the excipient combination of the formulations of the invention is a binder. Suitable binders are those that also function as a wicking or distributing agent in that they act to promote water intake into dosage forms made therefrom. Suitable binders include carbohydrates such as, microcrystalline cellulose, hydroxypropyl cellu-

lose, ethyl cellulose, starch, lactose, and also, mannitol and calcium phosphate. Microcrystalline cellulose is the preferred binder. Microcrystalline cellulose is commercially available as Avicel® PH (pharmaceutical grade) from FMC Corporation, Philadelphia, Pa., particularly Avicel® PH 101, PH 102, PH 103, PH 112, PH 200, PH 301, PH 302 and Ceolus. Microcrystalline cellulose is also available from Mendell, Penwest Company, Patterson, N.Y., as Emcocel® 90M and Emcocel® 50M, which could be used satisfactorily. Particularly preferred in the present formulations is Avicel® PH 102 or a combination of Avicel® PH 102 and Avicel® PH 200 as will be described below.

[0020] In a preferred embodiment of the present invention, the excipient combination of the present formulations comprises crospovidone as the superdisintegrant, calcium silicate as the dispersing agent, amorphous silica as the distributing agent and microcrystalline cellulose as the binder. The range of the members of the excipient combination of the subject formulations is from 4 to 8, preferably from 5 to 7, percent by weight of the superdisintegrant; from 20 to 70, preferably from 35 to 45, percent by weight of the dispersing agent; from 1 to 10, preferably from 1.5 to 3, percent by weight of the distributing agent; and from 10 to 50, preferably from 12 to 20, percent by weight of the binder, all based on the overall weight of the formulation including one or more medicaments. A particularly preferred excipient combination comprises 7 percent by weight of the superdisintegrant, 40 percent by weight of the dispersing agent, 2 percent by weight of the distributing agent and 15 percent by weight of the binder, based on the total weight of the formulation including medicament(s).

[0021] The formulations of the present invention may contain other conventional ingredients found in similar preparations known in the art and recognized as approved for use in preparations to be taken into the body. These would include, for example, natural and artificial flavors, polyols such as mannitol, sorbitol, maltitol and xylitol, artificial sweetening agents such as, N-α-L-Aspartyl-L-phenylalanine 1- methyl ester (aspartame) and 6-methyl-3,4-dihydro-1,2,3-oxathiazin-4(3H)-one-2,2-dioxide, particularly the potassium salt thereof (acesulfame K), flavor adjuncts such as tartaric acid, tabletting lubricants, such as magnesium stearate, and the like. Those skilled in the art of pharmaceutical compounding will appreciate that the amount of flavoring and sweetening agents, if any, present in the formulations of the present invention will be directly proportional to the taste or bitterness of the medicament. The flavoring and sweetening agents do not serve to coat the medicament, but are adequate to mask the objectionable taste of the medicaments in homogeneous admixture therewith. In general, the total of such conventional ingredients will not exceed 32 percent, preferably from 25 to 30 percent by weight based on the total weight of the formulation.

[0022] The medicament in the formulations of the present invention typically will not exceed 30 percent by weight, preferably from 1 to 15 percent by weight of the formulation. Those of ordinary skill in the art will appreciate that the physical characteristics of the medicament itself, i.e. its particle size and morphology, will directly influence its limiting content in the subject formulations. Clearly, there has to be sufficient medicament in the dosage form produced form the subject formulations to provide a therapeutically effective dosage. While solid dosage forms can be prepared from the formulations of the present invention by any recognized technique, including wet granulation, it is a particular advantage that the formulations can be dry granulated without the use of specialized equipment and conditions, thereby making them suitable for the formulation of medicaments that are sensitive to moisture and high temperatures.

[0023] Examples of medicaments that can be formulated into flash-melt tablets in accordance with the present invention include, without intended limitation, antihistamines, anti-motion sickness agents, analgesics, antiinflammatory agents, antibiotics, cholesterol lowering agents, anti-anxiety agents, anti-hypertensives, anti-cancer agents, hypnotics, anti-ulcer agents, coronary dilators, antivirals, anti-psychotics, anti-depressants, neuromuscular agents, anti-diarrheals, hypoglycemic agents, thyroid suppressors, anabolic agents, antisposmodics, antimigraine agents, diuretics, stimulants, decongestants, uterine relaxants, anti-arrhythmics, male erectile dysfunction compounds, Maxi-K channel openers or neuroprotective agents for the treatment of stroke or Alzheimer's disease and therapeutically appropriate combinations thereof. Specific therapeutic agents falling into the foregoing categories include, again without intended limitation, aripiprazole, ibuprofen, aspirin, acetaminophen, chlorpheniramine maleate, psuedoephedrine, diphenhydramine HCl, ranitidine, phenylpropanolamine, cimetidine, loperamide, meclizine, caffeine, entecavir, cefprozil, melatonergic agonists, pravastatin, captopril, fosinopril, irbesartan, omapatrilat, gatifloxacin and desquinolone and therapeutically appropriate combinations thereof.

[0024] As stated above, a decided advantage of the formulation of the present invention is that it can be dry-granulated into stable, fine granules that can be directly compressed into pharmaceutically elegant flash-melt oral dosage forms, e.g. tablets, caplets, wafers and the like. Preferably, the granules for flash-melt dosage forms in accordance with the present invention are formed in two steps. The process comprises initially forming granules, referred to herein as the intragranulation, by blending all of the medicament, the dispersing agent, distributing agent, other conventional ingredients as described above and a portion of each of the superdisintegrant, binder and tabletting lubricant together in a suitable mixer to assure uniform distribution throughout. A conventional V-blender is a preferred apparatus for this step. While a minor portion of the dispersing agent may be omitted from the intragranulation, it is preferred that all be incorporated therein. The blended mixture is then compacted in a conventional roller compactor having an orifice such that the compacts thereof are in the form of ribbons. Alternately, a slugging process can be used. The compacts from the roller compactor or the slugs from the slugger are passed through a fine screen, e.g. a 30 mesh (600 μm) screen, thereby

breaking them into granules between about 150 and 400 μm (microns) in size. The intragranulation granules thus-prepared are thereafter blended in a suitable mixer with the remaining ingredients, i.e., superdisintegrant, binder and lubricant, referred to herein as the extragranulation ingredients, to form a final blend that can be directly compressed into pharmaceutical dosage forms utilizing conventional equipment such as a tablet press. Rather than directly compress the final blend upon formation, since it is stable, it can be stored and subsequently pressed into dosage forms at a later time. It is a decided advantage of the subject invention that these operations are carried out without the need to resort to special handling such as taking precautions against any moisture coming in contact with the ingredients or the granules, and without the use of specially controlled temperature and humidity conditions.

[0025] The intragranulation comprises from 80 to 99, preferably from 85 to 95, most preferably 90, percent by weight of the final blend. Based on the weight of the final blend, the intragranulation preferably comprises up to 30 percent by weight, preferably from 6 to 20 percent by weight, of the binder, up to 5 percent by weight, preferably from 2 to 4 percent by weight, of the superdisintegrant, and all of the dispersing agent and the distributing agent. The binder and superdisintegrant are divided between the intragranulation and the extragranulation ingredients in weight ratios of approximately 2:1 to 4:1 for the binder and 0.5:2.0 to 2.0:0.5 for the superdisintegrant. The conventional tabletting lubricant is divided approximately equally between the intragranulation and the extragranulation ingredients.

[0026] The final blend is formed by mixing the intragranulation and the extragranulation components of the excipient combination, adding the remaining tabletting lubricant thereto and blending until uniform. Alternatively, a direct compression approach can be utilized in which all of the ingredients with the exception of the tabletting lubricant are mixed in a suitable blender, such as a conventional V-blender, by geometrically building the entire mass of the formulation via sequential blending for three minutes after each addition, and finally adding the lubricant to the mixture after all other ingredients have been blended.

[0027] Tablets compressed on a conventional tablet press from the final blend obtained from either a one-step granulation or a direct compression blend, were pharmaceutically elegant and disintegrated in water within ten seconds. A tablet is considered as disintegrated when it has totally broken down to granules and there are no discernible lumps remaining. Since the medicament is not intimately bound to any of the ingredients of the formulation, it is released within the same time period. The most outstanding advantage of the subject formulations is that dosage forms can be manufactured therefrom which are robust and, hence, avoid the need for specialized unit dose packaging and careful handling during manufacture or use as is often the case with present dosage forms. The dosage forms prepared from the formulations of the present invention can be packaged in conventional blister packs or in HDPE bottles. The invention is further described with reference to the following experimental work.

EXAMPLE 1

[0028] Flash-melt tablets were prepared as follows:

Intragranulation:

[0029]

Ingredient	Percent w/w	mg. per tablet
Xylitol (300) Xylisorb	26	52
Avicel® PH 102	12	24
Calcium Silicate	43.35	86.7
Crospovidone	3	6
Amorphous silica	2	4
Aspartame	2	4
Wild cherry flavor	0.15	0.3
Tartaric acid	2	4
Acesulfame K	2	4
Magnesium stearate	0.25	0.5
Total weight	92.75	185.5

[0030] The ingredients except for the magnesium stearate were blended in a commercial V-blender in geometric proportions for 5 minutes each until all were added. The magnesium stearate was then added and the mixture blended for an additional three minutes. The blended formulation was compacted at a pressure of 30-35 kg/cm^2 in a commercial compactor equipped with an orifice such that the compacts therefrom are in the form of ribbons. The ribbons were passed through a 30 mesh (600μm (microns)) screen to form stable granules of about 150 to 400 μm.

Extragranulation Ingredients:

[0031]

Ingredient	Percent w/w	mg per tablet
Intragranulation	92.75	185.5
Avicel® PH 200	3	6
Crospovidone	4	8
Magnesium stearate	0.25	0.5
Total weight	100	200

[0032] The intragranulation was placed in the blender and the Avicel® PH 200 and crospovidone added thereto and blended for five minutes. The magnesium stearate was then added and the mixture blended for an additional three minutes to form the final blend. Tablets compressed therefrom had a breaking force of 22.6 N (2.3 kP; 3.5 SCU) and disintegrated in 10 seconds in 5 ml of water. The final blend formulation demonstrated excellent flow and was free of other problems such as chipping, capping and sticking. It has been found that utilizing Avicel® PH 102 for the intragranulation and Avicel® PH 200 for the extragranulation ingredient enhanced the quality of the resultant tablets.

EXAMPLE 2

[0033] Flash-melt tablets containing a combination of two grades of calcium silicate were prepared as follows:

Intragranulation:

[0034]

Ingredient	Percent w/w	mg. per tablet
Xylitol (300) Xylisorb	26	52
Avicel® PH 102	12	24
Calcium Silicate (crystalline, alpha triclinic)	33.35	66.7
Hubersorb 600 NF (amorphous calcium silicate)	10	20
Crospovidone	3	6
Amorphous silica	2	4
Aspartame	2	4
Wild cherry flavor	0.15	0.3
Tartaric acid	2	4
Acesulfame K	2	4
Magnesium stearate	0.25	0.5
Total weight	92.75	185.5

[0035] The ingredients except for the magnesium stearate were blended in a commercial V-blender in geometric proportions for 5 minutes each until all were added. The magnesium stearate was added and the mixture blended for

an additional three minutes. The blended formulation was compacted, and screened to form stable granules in accordance with the procedure of Example 1.

Extragranulation Ingredients:

[0036]

Ingredient	Percent w/w	mg. per tablet
Intragranulation	92.75	185.5
Avicel® PH 200	3	6
Crospovidone	4	8
Magnesium stearate	0.25	0.5
Total weight	100	200

[0037] The intragranulation was placed in the blender and the Avicel® PH 200 and crospovidone added thereto and blended for five minutes. The magnesium stearate was then added and the mixture blended for an additional three minutes to from the final blend. Tablets compressed therefrom had a breaking force of 19.6N of (2.0 kP; 3.1 SCU) and disintegrated in 10 seconds in 5 ml of water.

EXAMPLE 3

[0038] Flash-melt tablets containing aripiprazole, an antischizophrenic drug, were prepared as follows:

Intragranulation

[0039]

Ingredient	Percent w/w	mg per tablet
Aripiprazole	15	30
Xylitol (300) Xylisorb	25	50
Avicel® PH 102	6	12
Calcium Silicate	37	74
Crospovidone	3	6
Amorphous silica	2	4
Aspartame	2	4
Wild cherry flavor	0.15	0.3
Tartaric acid	2	4
Acesulfame K	2	4
Magnesium stearate	0.25	0.5
Total weight	94.4	188.8

[0040] The ingredients except for the magnesium stearate were blended in a commercial V-blender in geometric proportions for 5 minutes each until all were added. The magnesium stearate was added and the mixture blended for an additional three minutes. The blended formulation was compacted, and screened to form stable granules in accordance with the procedure of Example 1.

Extragranulation Ingredients:

[0041]

Ingredient	Percent w/w	mg per tablet
Intragranulation	94.4	188.8
Avicel® PH 200	1.1	2.2
Crospovidone	4	8
Magnesium stearate	0.5	1
Total weight	100	200

[0042] The intragranulation was placed in the blender and the Avicel® PH 200 and crospovidone added thereto and blended for five minutes. The magnesium stearate was then added and the mixture blended for an additional three minutes to form the final blend. Tablets compressed therefrom had a breaking force of 19.6N of (2.0 kP; 3.1 SCU) and disintegrated in 10 seconds in 5 ml of water.

EXAMPLE 4

[0043] Flash-melt tablets containing aripiprazole were prepared as follows:

Intragranulation:

[0044]

Ingredient	Percent w/w	mg, per tablet
Aripiprazole	0.5	1
Xylitol (300) Xylisorb	27	54
Avicel® PH 102	12	24
Calcium Silicate	42	84
Crospovidone	3	6
Amorphous silica	2	4
Aspartame	2	4
Wild cherry flavor	0.15	0.3
Tartaric acid	2	4
Acesulfame K	2	4
Magnesium stearate	0.25	0.5
Total weight	92.9	185.8

[0045] The ingredients except for the magnesium stearate were blended in a commercial V-blender in geometric proportions for 5 minutes each until all were added. The magnesium stearate was added and the mixture blended for an additional three minutes. The blended formulation was compacted, and screened to form stable granules in accordance with the procedure of Example 1.

Extragranulation Ingredients:

[0046]

Ingredient	Percent w/w	mg. per tablet
Intragranulation	92.9	185.8
Avicel® PH 200	2.6	5.2
Crospovidone	4	8
Magnesium stearate	0.5	1
Total weight	100	200

[0047] The intragranulation was placed in the blender and the Avicel® PH 200 and crospovidone added thereto and blended for five minutes. The magnesium stearate was then added and the mixture blended for an additional three minutes to form the final blend. Tablets compressed therefrom had a breaking force of 22.6N (2.3 kP; 3.5 SCU) and disintegrated in 10 seconds in 5 ml of water.

EXAMPLE 5

[0048] Flash-melt tablets can be prepared containing the antiviral medicament entecavir as follows:

Intragranulation:

[0049]

Ingredient	Percent w/w	mg. per tablet
Entecavir	1	2
Xylitol (300) Xylisorb	26	52
Avicel® PH 102	10	20
Calcium Silicate	45	90
Crospovidone	4	8
Amorphous silica	2.	4
Aspartame	2	4
Wild cherry flavor	0.25	0.5
Tartaric acid	2	4
Acesulfame K	2.	4
Magnesium stearate	0.25	0.5
Total weight	94.5	189

[0050] The ingredients except for the magnesium stearate were blended in a commercial V-blender in geometric proportions for 5 minutes each until all were added. The magnesium stearate was added and the mixture blended for an additional three minutes. The blended formulation was compacted, and screened to form stable granules in accordance with the procedure of Example 1.

Extragranulation Ingredients:

[0051]

Ingredient	Percent w/w	mg. per tablet
Intragranulation	94.5	189
Avicel® PH 200	2	4
Crospovidone	3	6

Table continued

Ingredient	Percent w/w	mg. per tablet
Magnesium stearate	0.5	1
Total weight	100	200

[0052] The intragranulation was placed in the blender and the Avicel® PH 200 and crospovidone added thereto and blended for five minutes. The magnesium stearate was then added and the mixture blended for an additional three minutes to form the final blend. Tablets compressed therefrom had a breaking force of 22.6N (2.3 kP; 3.5 SCU) and disintegrated in 10 seconds in 5 ml of water. The percent w/w ratios taught in this example can also be used to formulate a suitable formulation of the present invention comprising 0.1 mg of entecavir per unit dose.

EXAMPLE 6

[0053] Flash-melt tablets can be prepared containing the antibiotic medicament cefprozil as follows:

Intragranulation:

[0054]

Ingredient	Percent w/w	mg. per tablet
Cefzil	25	125
Xylitol (300) Xylisorb	17	85
Avicel® PH 102	6	30
Calcium Silicate	35	175
Crospovidone	3	15
Amorphous silica	2	10
Aspartame	2	10
Wild cherry flavor	0.25	1.25
Tartaric acid	2	10
Acesulfame K	2	10
Magnesium stearate	0.25	1.25
Total weight	94.5	472.5

[0055] Blend the ingredients except for the magnesium stearate in a commercial V-blender in geometric proportions for 5 minutes each until all are added. Then add the magnesium stearate to the mixture prepared and mix for an additional three minutes. Then compact the blended formulation, and screen to form stable granules in accordance with the procedure of Example 1.

Extragranulation Ingredients:

[0056]

Ingredient	Percent w/w	mg per tablet
Intragranulation	94.5	472.5
Avicel® PH 200	2	10
Crospovidone	3	15
Magnesium stearate	0.5	2.5

Table continued

Ingredient	Percent w/w	mg per tablet
Total weight	100	500

[0057] Place the intragranulation in the blender and add the Avicel® PH 200 and crospovidone thereto and blend for five minutes. Then add magnesium stearate to the mixture and blend for an additional three minutes to form the final blend. Compress tablets therefrom to have a breaking force of 24.5N (2.5 kP; 3.8 SCU) and a disintegration time of 10 seconds or less in 5 ml of water.

EXAMPLE 7

[0058] Flash-melt tablets can be prepared containing the antihypertensive medicament irbesartan as follows:

Intragranulation:

[0059]

Ingredient	Percent w/w	mg per tablet
Irbesartan	25	125
Xylitol (300) Xylisorb	17	85
Avicel® PH 102	6.	30
Calcium Silicate	35	175
Crospovidone	3	15
Amorphous silica	2	10
Aspartame	2	10
Wild cherry flavor	0.25	1.25
Tartaric acid	2	10
Acesulfame K	2	10
Magnesium stearate	0.25	1.25
Total weight	94.5	472.5

[0060] Blend the ingredients except for the magnesium stearate in a commercial V-blender in geometric proportions for 5 minutes each until all are added. Then add the magnesium stearate to the mixture prepared and mix for an additional three minutes. Then compact the blended formulation, and screen to form stable granules in accordance with the procedure of Example 1.

Extragranulation Ingredients:

[0061]

Ingredient	Percent w/w	mg. per tablet
Intragranulation	94.5	472.5
Avicel® PH 20	2	10
Crospovidone	3	15
Magnesium stearate	0.5	2.5
Total weight	100	500

[0062] Place the intragranulation in the blender and add the Avicel® PH 200 and crospovidone thereto and blend for five minutes. Then add magnesium stearate to the mixture and blend for an additional three minutes to form the final blend. Compress tablets therefrom to have a breaking force of 24.5N (2.5 kP; 3.8 SCU) and a disintegration time of 10 seconds or less in 5 ml of water.

Reference Example 8

[0063] Flash-melt tablets can be prepared containing the quinolone antibiotic, des-Quinolone as follows:
Intragranulation:

Ingredient	Percent w/w	mg. per tablet
des-Quinolone	20.0	100
Xylitol (300) Xylisorb	22.0	110
Avicel® PH 102	6.0	30
Calcium Silicate	35.0	175
Crospovidone	3.0	15
Amorphous silica	2.0	10
Aspartame	2.0	10
Wild cherry flavor	0.25	1.25
Tartaric acid	2.0	10
Acesulfame K	2.0	10
Magnesium starate	0.25	1.25
Total weight	94.5	472.5

[0064] Blend the ingredients except for the magnesium stearate in a commercial V-blender in geometric proportions for 5 minutes each until all are added. Then add the magnesium stearate to the mixture prepared and mix for an additional three minutes. Then compact the blended formulation, and screen to form stable granules in accordance with the procedure of Example 1.

Extragranulation Ingredients:

[0065]

Ingredient	Percent w/w	mg. per tablet
Intragranulation	94.5	472.5
Avicel® PH 200	2.0	10.0
Crospovidone	3.0	15.0
Magnesium stearate	0.5	2.5
Total weight	100	500

[0066] Place the intragranulation in the blender and add the Avicel® PH 200 and crospovidone thereto and blend for five minutes. Then add magnesium stearate to the mixture and blend for an additional three minutes to form the final blend. Compress tablets therefrom to have a breaking force of 24.5 N (2.5 kP; 3.8 SCU) and a disintegration time of 10 seconds or less in 5 ml of water.

Example 9

[0067] Flash-melt tablets can be prepared containing the antibiotic gatifloxacin (Tequin®), as a taste masked co-

precipitate (30% w/w active) to deliver 50 mg dose:

Intragranulation:

[0068]

Ingredient	Percent w/w	mg. per tablet
Gatifloxacin:stearic acid co-precipitate	33.3	166.7
Xylitol (300) Xylisorb	11.7	58.5
Avicel® PH 102	6.0	30
Calcium Silicate	32.0	160
Crospovidone	3.0	15
Amorphous silica	2.0	10
Aspartame	2.0	10
Wild cherry flavor	0.25	1.23
Tartaric acid	2.0	10
Acesulfame K	2.0	10
Magnesium stearate	0.25	1.25
Total weight	94.5	472.5

[0069] Blend the ingredients except for the magnesium stearate in a commercial V-blender in geometric proportions for 5 minutes each until all are added. Then add the magnesium stearate to the mixture prepared and mix for an additional three minutes. Then compact the blended formulation, and screen to form stable granules in accordance with the procedure of Example 1.

Extragranulation Ingredients:

[0070]

Ingredient	Percent w/w	mg. per tablet
Intragranulation	94.5	472.5
Avicel® PH 200	2.0	10.0
Crospovidone	3.0	15.0
Magnesium stearate	0.5	2.5
Total weight	100	500

[0071] Place the intragranulation in the blender and add the Avicel® PH 200 and crospovidone thereto and blend for five minutes. Then add magnesium stearate to the mixture and blend for an additional three minutes to form the final blend. Compress tablets therefrom to have a breaking force of 24.5N (2.5 kP; 3.8 SCU) and a disintegration time of 10 seconds or less in 5 ml of water.

Claims

1. A flash-melt pharmaceutical dosage form that will disintegrate in the mouth In under 25 seconds, comprising a medicament and a combination of excipients which comprises, based on the total weight of the dosage form,

    a) from 4 to 8 % by weight of a superdisintegrant,

b) from 20 to 70 % by weight of a dispersing agent which is a calcium silicate,
c) from 1 to 10 % by weight of a distributing agent selected from amorphous silica, fumed silica, diatomaceous earth, talc, kaolin and magnesium aluminium trisilicate, and
d) from 10 to 50 % by weight of a binder.

2. A flash-melt pharmaceutical dosage form In accordance with claim 1, comprising not more than 30 percent by weight of the medicament, and not more than 85 percent by weight of the total of the combination of exdplents.

3. A flash-melt pharmaceutical dosage form according to claim 2, which, based on the total weight of said dosage form, comprises not more than about 30 percent by weight of said medicament, from 5 to 7 percent by weight of said superdisintegrant, from 35 to 45 percent by weight of said dispersing agent, from 1.5 to 3 percent by weight of said distributing agent and from 12 to 20 percent by weight of said binder.

4. A flash-melt pharmaceutical dosage form according to any one of the preceding claims, wherein the calcium silicate is selected from ortho, meta and alpha triclinic-calcium silicate.

5. A flash-melt pharmaceutical dosage form according to claim 4, wherein said calcium silicate is alpha triclinic-calcium silicate.

6. A flash-melt pharmaceutical dosage form according to any one of the preceding claims, wherein said superdisintegrant is crospovidone, croscarmellose sodium, sodium starch glycolate, low-substituted hydroxypropyl cellulose or pregelatinized starch, and said binder is microcrystalline cellulose, hydroxypropyl cellulose, ethyl cellulose, lactose, mannitol or calcium phosphate.

7. A flash-melt pharmaceutical dosage form according to claim 1. wherein said superdisintegrant is crospovidone, said calcium silicate is crystalline alpha triclinic-calcium silicate, said distributing agent is amorphous silica and said binderis microcrystalline cellulose.

8. A flash-melt pharmaceutical dosage form according to any one of claims 1 to 3, wherein said calcium silicate is comprised of a combination of alpha triclinic-calcium silicate and at least one other pharmaceutical grade of calcium silicate wherein said alpha triclinic-calcium silicate comprises from 10 % to 90 % by weight of said combination.

9. A flash-melt pharmaceutical dosage form according to any one of claims 1 to 4, wherein said calcium silicate has a surface area of 1.0 m^2/g (m^2/gm) to 210 m^2/g (m^2/gm) bulk density of 0.075 g/mL (g/cc) to 0.90 g/mL (g/cc), true density of 1.70 g/mL (g/cc) to 2.90 g/mL (g/cc) and volatile content of less than 1 % to 14 % w/w.

10. A flash-melt pharmaceutical dosage form according to daim 9, wherein said calcium sillcate is alpha triclinic-calcium silicate that has a surface area of 1.3 m^2/g (m^2/gm), bulk density of 0.627 g/mL (g/cc), true density of 2.934 g/mL (g/cc) and volatile content of 0.5 % w/w.

11. A flash-melt pharmaceutical dosage form according to claim 9, wherein said calcium silicate is ortho crystalline calcium silicate that has a surface area of 0.98 m^2/g (m^2/gm), baulk density of 0.492 g/mL (g/cc), true density of 3.252 g/mL (g/cc) and volatile content of 0.02 % w/w.

12. A flash-melt pharmaceutical dosage form according to claim 9. wherein said calcium silicate is meta crystalline calcium silicate that has a surface area of 1 2 2.5 m^2/g (m^2/gm), bulk density of 0.867 g/mL (g/cc), true density of 2.940 g/mL (g/cc) and volatile content of 0.5%w/w.

13. A flash-melt pharmaceutical dosage form according to claim 9, wherein said calcium silicate is crystalline calcium silicate that has a surface area of 90.4 m^2/g (m^2/gm), bulk density of 0.094 g/mL (g/cc), true density of 2.598 g/mL (g/cc) and volatile content of 0.94 % w/w.

14. A flash-melt pharmaceutical dosage form according to claim 9, wherein said calcium silicate is amorphous calcium silicate that has a surface area of 191.3 m^2/g (m^2/gm), bulk density of 0.120 g/mL (g/cc), true density of 2.314 g/mL (g/cc) and volatile content of 5.11 % w/w.

15. A flash-melt pharmaceutical dosage form according to claim 9, wherein said calcium silicate is amorphous calcium silicate that has a surface area of 103.0 m^2/g (m^2/gm), bulk density of 0.130 g/mL (g/cc), true density of 1.702 g/mL

(g/cc) and volatile content of 9.90% w/w.

16. A flash-melt pharmaceuttcal dosage form according to daim 9, wherein said calcium stlicate is amorphous calcium silicate that has a surface area of 209 m^2/g (m^2/gm), bulk density of 0.075 g/mL (g/cc), true density of 2.035 g/mL (g/cc) and volatile content of 13.8 % w/w.

17. A flash-melt pharmaceutical dosage form according to any one of the preceding claims. wherein said medicament is aripiprazole.

18. A flash-melt pharmaceutical dosage form according to any one of the preceding claims, which is a tablet.

19. A flash-melt pharmaceutical dosage form according to claim 1 obtainable by dry blending into mixture, a medicament and a combination of excipients as defined In any one of claims 1 to 18, compressing the mixture through a suitable compactor or slugger to form compacts or slugs and passing the compacts or slugs through a screen to form granules.

20. A flash-melt pharmaceutical dosage form according to claim 19, obtainable by further compressing the granules.

21. A method of forming granules suitable for compressing into flash-melt dosage forms according to any one of claims 1 to 20, comprising dry blending into a mixture a medicament, and a combination of excipients as defined in any one of claims 1 to 20, compressing the mixture through a suitable compactor or slugger to form compacts or slugs and passing the compacts or slugs through a screen to form granules.

22. A method of forming granules according to claim 21, additionally comprising the step of blending said granules with additional quantities of said superdisintegrant and binder to form a final blend suitable for direct compression into said tablets.

23. A method according to claim 22, wherein said granules comprise from about 80 % to about 99 % by weight of said final blend.

Patentansprüche

1. Pharmazeutische Flash-melt-Dosierungsform, die im Mund in weniger als 25 Sekunden zerfällt, umfassend ein Medikament und eine Kombination aus Exzipienten, die, bezogen auf das Gesamtgewicht der Dosierungsform, umfassen

   a) 4 bis 8 Gew.-% eines Superdisintegrationsmittels,
   b) 20 bis 70 Gew.-% eines Dispergiermittels, bei dem es sich um ein Calciumsilikat handelt,
   c) 1 bis 10 Gew.-% eines Distributionsmittels, ausgewählt unter amorphem Siliciumdioxid, pyrogenes Siliciumdioxid, Diatomeenerde, Talkum, Kaolin und Magnesiumaluminiumtrisilikat und
   d) 10 bis 50 Gew.-% eines Bindemittels.

2. Pharmazeutische Flash-melt-Dosierungsform nach Anspruch 1, umfassend nicht mehr als 30 Gew.-% des Medikaments und nicht mehr als 85 % der Kombination an Exzipienten am Gesamtgewicht.

3. Pharmazeutische Flash-melt-Dosierungsform nach Anspruch 2, die, bezogen auf das Gesamtgewicht der Dosierungsform, nicht mehr als etwa 30 Gew.-% des erwähnten Medikaments, 5 bis 7 Gew.-% des erwähnten Superdisintegrationsmittels, 35 bis 45 Gew.-% des erwähnten Dispergiermittels, 1,5 bis 3 Gew.-% des erwähnten Distributionsmittels und 12 bis 20 Gew.-% des erwähnten Bindemittels umfasst.

4. Pharmazeutische Flash-melt-Dosierungsform nach einem der vorhergehenden Ansprüche, wobei das Calciumsilikat ausgewählt ist unter ortho-, meta- und triklinem α-Calciumsilikat.

5. Pharmazeutische Flash-melt-Dosierungsform nach Anspruch 4, wobei das erwähnte Calciumsilikat triklines α-Calciumsilikat ist.

6. Pharmazeutische Flash-melt-Dosierungsform nach einem der vorhergehenden Ansprüche, wobei das Superdisintegrationsmittel Crospovidon, Croscarmellose-Natrium, Natrium-Stärkeglykolat, niedrigsubstituierte Hydroxypropyl-

cellulose oder vorverkleisterte Stärke ist und das erwähnte Bindemittel mikrokristalline Cellulose, Hydroxypropylcellulose, Ethylcellulose, Laktose, Mannit oder Calciumphosphat ist.

7. Pharmazeutische Flash-melt-Dosierungsform nach Anspruch 1, wobei das erwähnte Superdisintegrationsmittel Crospovidon ist, das erwähnte Calciumsilikat kristallines triklines α-Calciumsilikat ist, das erwähnte Distributionsmittel amorphes Siliciumdioxid ist und das erwähnte Bindemittel mikrokristalline Cellulose ist.

8. Pharmazeutische Flash-melt-Dosierungsform nach einem der Ansprüche 1 bis 3, wobei das erwähnte Calciumsilikat eine Kombination aus triklinem α-Calciumsilikat und wenigstens einem weiteren Calciumsilikat pharmazeutischer Qualität umfasst, wobei das erwähnte trikline α-Calciumsilikat 10 bis 90 Gew.-% der Kombination ausmacht.

9. Pharmazeutische Flash-melt-Dosierungsform nach einem der Ansprüche 1 bis 4, wobei das erwähnte Calciumsilikat eine Oberfläche von 1,0 m^2/g (m^2/gm) bis 210 m^2/g (m^2/gm), eine Schüttdichte von 0,075 g/ml (g/cc) bis 0,90 g/ml (g/cc), eine echte Dichte von 1,70 g/ml (g/cc) bis 2,90 g/ml (g/cc) und einen Gehalt an flüchtigen Bestandteilen von weniger als 1 % bis 14 % w/w aufweist.

10. Pharmazeutische Flash-melt-Dosierungsform nach Anspruch 9, wobei das erwähnte Calciumsilikat triklines α-Calciumsilikat ist, das eine Oberfläche von 1,3 m^2/g (m^2/gm), eine Schüttdichte von 0,627 g/ml (g/cc), eine echte Dichte von 2,934 g/ml (g/cc) und einen Gehalt an flüchtigen Bestandteilen von 0,5 % w/w aufweist.

11. Pharmazeutische Flash-melt-Dosierungsform nach Anspruch 9, wobei das erwähnte Calciumsilikat kristallines ortho-Calciumsilikat ist, das eine Oberfläche von 0,98 m^2/g (m^2/gm), eine Schüttdichte von 0,492 g/ml (g/cc), eine echte Dichte von 3,252 g/ml (g/cc) und einen Gehalt an flüchtigen Bestandteilen von 0,02 % w/w aufweist.

12. Pharmazeutische Flash-melt-Dosierungsform nach Anspruch 9, wobei das erwähnte Calciumsilikat kristallines meta-Calciumsilikat ist, das eine Oberfläche von 2,5 m^2/g (m^2/gm), eine Schüttdichte von 0,867 g/ml (g/cc), eine echte Dichte von 2,940 g/ml (g/cc) und einen Gehalt an flüchtigen Bestandteilen von 0,5 % w/w aufweist.

13. Pharmazeutische Flash-melt-Dosierungsform nach Anspruch 9, wobei das erwähnte Calciumsilikat kristallines Calciumsilikat ist, das eine Oberfläche von 90,4 m^2/g (m^2/gm), eine Schüttdichte von 0,094 g/ml (g/cc), eine echte Dichte von 2,596 g/ml (g/cc) und einen Gehalt an flüchtigen Bestandteilen von 0,94 % w/w aufweist.

14. Pharmazeutische Flash-melt-Dosierungsform nach Anspruch 9, wobei das erwähnte Calciumsilikat amorphes Calciumsilikat ist, das eine Oberfläche von 191,3 m^2/g (m^2/gm), eine Schüttdichte von 0,120 g/ml (g/cc), eine echte Dichte von 2,314 g/ml (g/cc) und einen Gehalt an flüchtigen Bestandteilen von 5,11 % w/w aufweist.

15. Pharmazeutische Flash-melt-Dosierungsform nach Anspruch 9, wobei das erwähnte Calciumsilikat amorphes Calciumsilikat ist, das eine Oberfläche von 103,0 m^2/g (m^2/gm), eine Schüttdichte von 0,130 g/ml (g/cc), eine echte Dichte von 1,702 g/ml (g/cc) und einen Gehalt an flüchtigen Bestandteilen von 9,90 % w/w aufweist.

16. Pharmazeutische Flash-melt-Dosierungsform nach Anspruch 9, wobei das erwähnte Calciumsilikat amorphes Calciumsilikat ist, das eine Oberfläche von 209 m^2/g (m^2/gm), eine Schüttdichte von 0,075 g/ml (g/cc), eine echte Dichte von 2,035 g/ml (g/cc) und einen Gehalt an flüchtigen Bestandteilen von 13,8 % w/w aufweist.

17. Pharmazeutische Flash-melt-Dosierungsform nach einem der vorhergehenden Ansprüche, wobei das Medikament Aripiprazol ist.

18. Pharmazeutische Flash-melt-Dosierungsform nach einem der vorhergehenden Ansprüche, bei der es sich um eine Tablette handelt.

19. Pharmazeutische Flash-melt-Dosierungsform nach Anspruch 1, erhältlich indem ein Medikament und eine Kombination an Exzipienten wie in einem der Ansprüche 1 bis 18 definiert trocken zu einem Gemisch vermischt werden, das Gemisch durch einen geeigneten Kompaktor oder eine geeignete Formvorrichtung unter Bildung von kompaktierten Teilchen oder Formlingen komprimiert wird und die kompaktierten Teilchen oder Formlinge durch ein Sieb gegeben werden, wobei ein Granulat gebildet wird.

20. Pharmazeutische Flash-melt-Dosierungsform nach Anspruch 19, erhältlich indem das Granulat zusätzlich komprimiert wird.

21. Verfahren zur Bildung eines Granulats, das zur Komprimierung in die Flash-melt-Dosierungsformen nach einem der Ansprüche 1 bis 20 geeignet ist, wobei ein Medikament und eine Kombination an Exzipienten wie in einem der Ansprüche 1 bis 20 definiert trocken zu einem Gemisch vermischt werden, das Gemisch durch einen geeigneten Kompaktor oder eine geeignete Formvorrichtung zu kompaktierten Teilchen oder Formlingen komprimiert wird und die kompaktierten Teilchen oder Formlinge durch ein Sieb gegeben werden, wobei das Granulat gebildet wird.

22. Verfahren zur Bildung eines Granulats nach Anspruch 21, das zusätzlich den Schritt des Vermischens des Granulats mit weiteren Mengen an Superdisintegrationsrmittel und Bindemittel umfasst, wobei ein Endgemisch gebildet wird, das zur Direktkomprimierung in die erwähnten Tabletten geeignet ist.

23. Verfahren nach Anspruch 22, wobei das Granulat etwa 80 bis etwa 99 Gew.-% des erwähnten Endgemisches ausmacht.

Revendications

1. Forme de dosage pharmaceutique fondant très rapidement qui se désintégrera dans la bouche en moins de 25 secondes, comprenant un médicament et une combinaison d'excipients qui comprend, en se basant sur le poids total de la forme de dosage,

   a) de 4 à 8 % en poids d'un superdésintégrant,
   b) de 20 à 70 % en poids d'un agent dispersant qui est du silicate de calcium,
   c) de 1 à 10 % en poids d'un agent de distribution sélectionné parmi silice amorphe, silice fumée, diatomite, talc, kaolin et trisilicate de magnésium aluminium, et
   d) de 10 à 50 % en poids d'un liant.

2. Forme de dosage fondant très rapidement selon la revendication 1, ne comprenant pas plus de 30 % en poids du médicament, et pas plus de 85 % en poids du total de la combinaison des excipients.

3. Forme de dosage pharmaceutique fondant très rapidement selon la revendication 2 qui, en se basant sur le poids total de ladite forme de dosage, ne comprend pas plus d'environ 30 % en poids dudit médicament, de 5 à 7 % en poids dudit agent superdésintégrant, de 35 à 45 % en poids dudit agent dispersant, de 1,5 à 3 % en poids dudit agent de distribution et de 12 à 20 % en poids dudit liant.

4. Forme de dosage pharmaceutique fondant très rapidement selon l'une quelconque des revendications précédentes, où le silicate de calcium est sélectionné parmi ortho, méta et alpha silicate de calcium triclinique.

5. Forme de dosage pharmaceutique fondant très rapidement selon la revendication 4, où ledit silicate de calcium est de l'alpha silicate de calcium triclinique.

6. Forme de dosage fondant très rapidement selon l'une quelconque des revendications précédentes, où ledit superdésintégrant est crospovidone, croscarmellose sodium, glycolate de sodium amidon, hydroxypropyl cellulose faiblement substituée ou amidon prégélatinisé, et ledit liant est cellulose microcristalline, hydroxypropyl cellulose, éthyl cellulose, lactose, mannitol ou phosphate de calcium.

7. Forme de dosage fondant très rapidement selon la revendication 1, où ledit superdésintégrant est crospovidone, ledit silicate de calcium est alpha silicate de calcium triclinique cristallin, ledit agent de distribution est de la silice amorphe et ledit liant est de la cellulose microcristalline.

8. Forme de dosage pharmaceutique fondant très rapidement selon l'une quelconque des revendications 1 à 3, où ledit silicate de calcium se compose d'une combinaison d'alpha silicate de calcium triclinique et d'au moins une autre qualité pharmaceutique de silicate de calcium, où ledit alpha silicate de calcium triclinique forme 10 à 90 % en poids de ladite combinaison.

9. Forme de dosage pharmaceutique fondant très rapidement selon l'une quelconque des revendications 1 à 4, où ledit silicate de calcium a une aire superficielle de 1,0 m^2/g (m^2/gm) à 210 m^2/g (m^2/gm) , une densité apparente de 0,075 g/mℓ (g/cc) à 0,90 g/ mℓ (g/cc), une densité réelle de 1,70 g/ mℓ (g/cc) à 2,90 g/ mℓ (g/cc) et une teneur en produits volatils de moins de 1 % à 14 % p/p.

10. Forme de dosage pharmaceutique fondant très rapidement selon la revendication 9, où ledit silicate de calcium est de l'alpha silicate de calcium triclinique qui a une aire superficielle de 1,3 m^2/g (m^2/gm), une densité apparente de 0,627 g/ mℓ (g/cc), une densité réelle de 2,934 g/ mℓ (g/cc) et une teneur en produits volatils de 0,5 % p/p.

11. Forme de dosage pharmaceutique fondant très rapidement selon la revendication 9, où ledit silicate de calcium est de l'ortho silicate de calcium cristallin qui a une aire superficielle de 0,98 m^2/g (m^2/gm) , une densité apparente de 0,492 g/ mℓ (g/cc), une densité réelle de 3,252 g/ mℓ (g/cc) et une teneur en produits volatils de 0,02 % p/p.

12. Forme de dosage pharmaceutique fondant très rapidement selon la revendication 9, où ledit silicate de calcium est du méta silicate de calcium cristallin qui a une aire superficielle de 2,5 m^2/g (m^2/gm), une densité apparente de 0,867 g/ mℓ (g/cc), une densité réelle de 2,940 g/ mℓ (g/cc) et une teneur en produits volatils de 0,5 % p/p.

13. Forme de dosage pharmaceutique fondant très rapidement selon la revendication 9, où ledit silicate de calcium est du silicate de calcium cristallin, qui a une aire superficielle de 90,4 m^2/g (m^2/gm), une densité apparente de 0,094 g/ mℓ (g/cc), une densité réelle de 2,596 g/ mℓ (g/cc) et une teneur en produits volatils de 0,94 % p/p.

14. Forme de dosage pharmaceutique fondant très rapidement selon la revendication 9, où ledit silicate de calcium est du silicate de calcium amorphe, qui a une aire superficielle de 191,3 m^2/g (m^2/gm), une densité apparente de 0,120 g/ mℓ (g/cc), une densité réelle de 2,314 g/ mℓ (g/cc) et une teneur en produits volatils de 5,11 % p/p.

15. Forme de dosage pharmaceutique fondant très rapidement selon la revendication 9, où ledit silicate de calcium est du silicate de calcium amorphe, qui a une aire superficielle de 103,0 m^2/g (m^2/gm), une densité apparente de 0,130 g/ mℓ (g/cc), une densité réelle de 1,702 g/ mℓ (g/cc) et une teneur en produits volatils de 9,90 % p/p.

16. Forme de dosage pharmaceutique fondant très rapidement selon la revendication 9, où ledit silicate de calcium est du silicate de calcium amorphe, qui a une aire superficielle de 209 m^2/g (m^2/gm), une densité apparente de 0,075 g/ me (g/cc), une densité réelle de 2,035 g/ mℓ (g/cc) et une teneur en produits volatils de 13,8 % p/p.

17. Forme de dosage pharmaceutique fondant très rapidement selon l'une quelconque des revendications précédentes, où ledit médicament est aripiprazole.

18. Forme de dosage pharmaceutique fondant très rapidement selon l'une quelconque des revendications précédentes, qui est un comprimé.

19. Forme de dosage pharmaceutique fondant très rapidement selon la revendication 1, que l'on peut obtenir par mélange à sec, en un mélange, d'un médicament et d'une combinaison d'excipients comme défini dans l'une quelconque des revendications 1 à 18, compression du mélange à travers un compacteur ou lingoteur approprié pour former des compacts ou des lingots et passage des compacts ou lingots à travers un tamis pour former des granules.

20. Forme de dosage fondant très rapidement selon la revendication 19, que l'on peut obtenir en comprimant encore les granulés.

21. Méthode de formation de granules appropriés pour une compression en forme de dosage fondant très rapidement selon l'une quelconque des revendications 1 à 20, comprenant un mélange à sec, en un mélange, d'un médicament et d'une combinaison d'excipients comme défini dans l'une quelconque des revendications 1 à 20, compression du mélange à travers un compacteur ou lingoteur approprié pour former des compacts ou lingots et passage des compacts ou lingots à travers un tamis pour former des granules.

22. Méthode de formation de granules selon la revendication 21, comprenant additionnellement l'étape de mélanger lesdits granules avec des quantités additionnelles dudit superdésintégrant et du liant pour former un mélange final approprié à une compression directe en lesdits comprimés.

23. Méthode selon la revendication 22, où les granules comprennent environ 80 % à environ 99 % en poids dudit mélange final.